IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Isa Odidi *et al.*

Application No.: 09/166,701 Confirmation No.: 9432

Filed: October 5, 1998 Art Unit: 1614

For: CONTROLLED RELEASE PHARMACEUTICAL DELIVERY DEVICE AND PROCESS FOR PREPARATION THEREOF

Examiner: S. V. Gembeh

APPEAL BRIEF

To the Commissioner for Patents:

Appellants submits this brief in support of the appeal initiated by a Notice of Appeal filed on January 15, 2010. The appeal brief fee pursuant to C.F.R. § 41.20(b)(2) is submitted herewith. For the reasons set forth in this brief, Appellants respectfully request the Board of Patent Appeals and Interferences to reverse the Examiner's final rejection of the claimed subject matter.

(1) Real Party in Interest

The real party in interest in this appeal is Intellipharmaceutics Corp., the Assignee of record.

(2) Related Appeals and Interferences

There are no other appeals or interferences known to Appellant, the Attorneys/Agents or record, or the Assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

(3) Status of Claims

The application has a total of 36 claims. Of these, claims 1, 4, 7-9, 11, 12, 23, 28-31 and 33-36 and are pending, and claims 2-3, 5-6, 10, 13-22, 24-27 and 32 have previously been canceled. Claims 1, 4, 7-9, 11, 12, 23, 28-31 and 33-36 stand rejected and are on appeal.

(4) Status of Amendments

A response was filed after the final rejection that led to this appeal, along with terminal disclaimers over U.S. Pat. No. 7,090,867 and U.S. Application No. 11/473,386 were filed on January 15, 2010, along with the Notice of Appeal. As indicated in the Advisory Action mailed on February 26, 2010, the response was entered indicating that the non-statutory obviousness-type double patenting rejections were obviated by the terminal disclaimers, while the 35 U.S.C. § 103 rejections were maintained.

(5) Summary of Claimed Subject Matter

The subject matter of independent claim 1 is a controlled release pharmaceutical delivery composition which provides sustained delivery of a pharmaceutically active substance for a predetermined period of time (Specification at p. 1, ll. 6-8), said composition comprising: about 1-50% by weight polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol (Id. at p. 2, ll. 25-26; p. 4, ll. 27-29); about 1 to 58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose (Id. at p. 2 l. 27 and 32; p. 3, ll. 1-2; p. 5, ll. 4-6; p. 7, l. 14 and 16); between 0 and 10 % by weight talc (Id. at p. 3, ll. 4); between 0 and 10 % by weight magnesium stearate (Id. at p. 3, ll. 5); and about 1-80% by weight of a pharmaceutically active agent (Id. at p. 3, l. 10); wherein said acrylic acid crosslinked polymers, hydroxyethyl cellulose and hydroxypropyl

methylcellulose, talc, magnesium stearate and pharmaceutically active agent are provided as a homogenous mixture (Id. at p. 5, l. 1-8; p. 7, ll. 20-25; p. 8, ll. 4-9 and 23-30).

The subject matter of independent claim 9 is a controlled release pharmaceutical delivery composition which provides sustained delivery of a pharmaceutically active substance for a predetermined period of time (Id. at p. 1, ll. 6-8), said composition comprising: about 1 to 58% by weight of a mixture of hydroxyethylcellulose and hydroxypropylmethyl cellulose (Id. at p. 2 l. 27 and 32; p. 3, ll. 1-2; p. 5, ll. 4-6; p. 7, l. 14 and 16); about 1 to 60% by weight of ethyl cellulose (Id. at p. 4, ll. 4); about 1 to 80% by weight of at least one carboxyvinyl polymer resin (Id. at p. 4, ll. 7; p. 4, ll. 27-31); between 0 and 10% by weight of talc (Id. at p. 4, ll. 8); between 0 and 10% by weight of magnesium stearate (Id. at p. 4, ll. 9); between 0 and 95% by weight granulating and tableting aids (Id. at p. 4, ll. 10); and about 1-80% of a pharmaceutically active agent (Id. at 4. 3, l. 3), wherein said hydroxyethylcellulose, hydroxypropylmethyl cellulose, ethylcellulose, carboxyvinyl polymer resin, talc, magnesium stearate, granulating and tableting aid, and pharmaceutically active agent are provided as a matrix (Id. at p. 4, ll. 20-22; p. 5, l. 1-8; p. 7, ll. 20-25; p. 8, ll. 4-9 and 23-30).

The subject matter of independent claim 23 is a pharmaceutical composition comprising: about 1 to 80% by weight pharmaceutically active agent (Id. at p. 4, l. 3).; about 1 to 50% by weight of polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol (Id. at p. 2, ll. 25-26; p. 4, ll. 27-29); and about 1 to 58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose (Id. at p. 2 l. 27 and 32; p. 3, ll. 1-2; p. 5, ll. 4-6; p. 7, l. 14 and 16).; wherein said polymers of acrylic acid, hydroxyethyl cellulose and hydroxypropyl methyl cellulose, and pharmaceutically active

agent are provided as a homogenous mixture (Id. at p. 4, ll. 20-22; p. 5, l. 1-8; p. 7, ll. 20-25; p. 8, ll. 4-9 and 23-30).

The subject matter of independent claim 30 is a pharmaceutical composition comprising: about 1 to 80% pharmaceutically active agent (Id. at p. 4, l. 3); about 1 to 58% by weight of hydroxyethylcellulose and hydroxypropylmethyl cellulose (Id. at p. 2 l. 27 and 32; p. 3, ll. 1-2; p. 5, ll. 4-6; p. 7, l. 14 and 16); about 1 to 60% by weight of ethylcellulose (Id. at p. 3, ll. 2); about 1 to 50% by weight of at least one carboxyvinyl polymer resin (Id. at p. 2, ll. 25-26; p. 4, ll. 27-29); between 0 and 10% by weight of talc (Id. at p. 4, ll. 8); between 0 and 10% by weight of magnesium stearate (Id. at p. 4, ll. 9); and between 0 and 95% by weight granulating and tableting aids (Id. at p. 4, l. 10), wherein said pharmaceutically active agent, hydroxyethyl cellulose and hydroxypropyl methylcellulose, ethylcellulose, talc, magnesium stearate, and granulating and tableting aids, are provided as a homogenous mixture (Id. at p. 4, ll. 20-22; p. 5, l. 1-8; p. 7, ll. 20-25; p. 8, ll. 4-9 and 23-30).

The subject matter of independent claim 33 is a pharmaceutical composition comprising: about 1 to 80% by weight pharmaceutically active agent (Id. at p. 2, ll. 25-26); about 1 to 50% by weight of polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol (Id. at p. 2, ll. 25-26; p. 4, ll. 27-29); about 1 to 58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose (Id. at p. 2, l. 27 and 32; p. 3, ll. 1-2; p. 5, ll. 4-6; p. 7, l. 14 and 16); wherein said polymers of acrylic acid, hydroxyethyl cellulose and hydroxypropyl methylcellulose and the pharmaceutically active agent are provided as a homogenous mixture (Id. at p. 4, ll. 20-22; p. 5, l. 1-8; p. 7, ll. 20-25; p. 8, ll. 4-9 and 23-30); and about 0.5 to 50% by weight of a coating material coating said matrix, said coating material comprising anionic polymers based on methacrylic acid and

methacrylic acid esters or neutral methacrylic acid esters with trimethylammonioethyl methacrylate chloride or cellulose esters (Id. at p. 6, ll. 1-4).

(6) Grounds of Rejection to be Reviewed on Appeal

Appellants submit one ground of rejection for review: that the subject matter of claims 1, 4, 7-9, 11, 12, 23, 28-31 and 33-36 is obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 4,242,786 to Weiss et al. ("Weiss") in view of U.S. Patent No. 4,940,587 to Jenkins et al. ("Jenkins").

(7) Argument

The Examiner has rejected claims 1, 4, 7-9, 11, 12, 23, 28-31 and 33-36 as being allegedly obvious over U.S. Patent No. 4,252,786 to Weiss et al. ("Weiss") in view of U.S. Patent No. 4,940,587 to Jenkins et al. ("Jenkins"). For the reasons set forth below, it is the Appellants position that one of ordinary skill in the art would not have been motivated to combine the cited references to produce the claimed invention with any reasonable expectation of success, nor would the claimed invention have been obvious to try.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion

of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." Fed. Reg. Vol. 72, No. 195 at p. 57528. Additionally, objective evidence of nonobviousness must be considered. Such evidence, sometimes referred to as ''secondary considerations,'' may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *Id.*

It is the Examiner's position that "[a]lthough Weiss teaches the combination of hydroxymethyl cellulose and hydroxypropylmethyl cellulose, they do not teach the recited combined concentration; however Jenkins teaches the polymer mixture 'Natrosol 250' as described in the instant specification." *Final Office Action* at p. 3. The Examiner's interpretation of Weiss and Jenkins is incorrect, as set forth below.

Weiss describes a tablet having a polymeric vinylpyrrolidinone carboxyvinyl hydrophilic core coated with a relatively insoluble, water permeable film, wherein the film comprises a combination of hydrophobic and hydrophilic polymers. *Weiss* at col. 1, ll. 38-48. The hydrophilic polymers can be cellulose methyl ethers, including hydroxypropylmethyl cellulose. *Id.* at col. 3, ll. 65-67.

Importantly, Weiss fails to disclose 1-58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose provided as a homogenous mixture with the other tablet ingredients, as recited in the amended claims. Specifically, the hydroxypropyl methylcellulose described in Weiss is provided as a part of a coating solution, which is applied to the exterior of the tablet, and is not a part of the core containing the active ingredient. Carbopol 934, meanwhile, is a part of the Weiss tablet core. Thus, these two

ingredients cannot be considered to be "provided as a homogenous mixture," as recited in the instant claims.

Jenkins fails to remedy the deficiencies of Weiss. The Examiner states that "Jenkins teaches the same polymer mixture 'Natrosol 250' as described in the instant specification. Thus it is reasonable to assume the 'Natrosol 250' comprises the percentages required for hydroxymethyl cellulose and hydroxypropyl methylcellulose." *Final Office Action mailed on July 17, 2009*, at p. 3. This statement is incorrect. Natrosol 250 is not a mixture of hydroxymethyl cellulose and hydroxypropylmethyl cellulose in the presently claimed amounts. Rather, Natrosol 250 is a commercially available brand of hydroxy ethylcellulose. *Specification* at p. 5, ll. 4-7. As explained in the present specification, the hydroxyethyl cellulose can be Natrosol 250, while the hydroxypropylmethyl cellulose can be Methocel premium grade type K100M CR. *Id.* Thus, Jenkins also fails to disclose a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose.

Furthermore, Appellants have demonstrated that the types of cellulose used in the formulation are not interchangeable. For example, in the Declaration under C.F.R. § 1.132 by Odidi et al. submitted on September 21, 2004, as Attachment 1 (Evidence Appendix A), Appellants demonstrated dramatically different release rates in compositions comprising 15 % hydroxypropylmethyl cellulose, 15% hydroxymethyl cellulose and 15% ethyl cellulose. Specifically, the amount of drug released after 1 hour was about 17% for hydroxypropylmethyl cellulose, 60 % for hydroxyethyl cellulose and 88 % for ethyl cellulose. *Evidence Appendix A* at table 2 and paragraph 5. A formulation comprising 7.5 % hydroxypropyl cellulose and 7.5 % hydroxypropylmethyl cellulose was compared with

a formulation comprising 7.5 % hydroxymethyl cellulose and 7.5 % hydroxypropylmethyl cellulose was provided in the Declaration under C.F.R. § 1.132 by Odidi et al. submitted on September 21, 2004, as Attachment 2 (Evidence Appendix B). This data also demonstrated significantly different release profiles between these formulations. *Evidence Appendix B* at table 2, figure 1 and paragraphs 4-6.

Furthermore, the pharmaceutical composition of Jenkins contains "granules of a higher aliphatic alcohol and a hydrated water-soluble hydroxyalkyl cellulose having a drug distributed therethrough and being coated with a cellulose derivative which is adherent to the mucosa." *Jenkins* at col. 1, ll. 51-56 (emphasis added). Thus, like Weiss, Jenkins also maintains the cellulose in the coating, while the active drug agent is provided in the core, rather than providing them together as a homogenous mixture as claimed. Jenkins and Weiss, either alone or in combination, further fail to provide any motivation to provide the ingredients as presently claimed with any reasonable expectation success.

As described in the Declaration under C.F.R. § 1.132 by Odidi et al. submitted on May 15, 2009 (Evidence Appendix C), the form in which the ingredients of the pharmaceutical composition are provided has an effect on its release profile. The present claims provide all of the recited components as a homogenous mixture, which is then formulated into a tablet. The resulting tablet has distinct release profile that is not achieved by, nor suggested by, the teachings of Weiss and Jenkins, which separate certain components into a coating. Specifically, the Declaration describes a comparative experiment between a tablet prepared according to Weiss and a tablet prepared according to the present invention, each containing Metformin as the pharmaceutical ingredient. *Evidence Appendix C* at ¶¶ 6-7; Tables 1-3. The dissolution of each of the tablets was

then studied over a 13 hour period of time, and were shown to have different release profiles. The results demonstrate that the Weiss tablet releases the Metformin in two steps. First, there is a lag phase for almost an hour, followed by a relatively fast rate of release. *Appendix A* at ¶ 10; Table 5; Figure 1. In contrast, the tablet from the present application provides a one step process, wherein the drug begins to be released almost immediately, and continues to be released at a relatively steady rate, over a longer period of time compared to the Weiss tablet. *Appendix A* at ¶ 11; Table 5; Figure 1. As depicted in Figure 1 of the Declaration, nearly 100 % of the drug is released by the Weiss tablet at 4 hours, while a little over 80 % of the drug is released by the claimed formulation at 4 hours. Thus, the presently claimed formulation provides unexpected results over Weiss.

As explained above, the cited references, either alone or in combination, fail to teach or suggest a pharmaceutical delivery composition comprising about 1-50 % by weight of polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol, 1 to 58 % by weight mixture of hydroxymethyl cellulose and hydroxypropylmethyl cellulose, wherein all of the recited ingredients are provided as a homogenous mixture. The Examiner has not provided any rational basis for preparing the claimed composition, either based on the teachings of Weiss and Jenkins or based on the knowledge in the art such that it would be "obvious to try" to prepare the claimed composition. *KSR*. For at least these reasons, Appellants respectfully request withdrawal of this rejection.

CONCLUSION

For the reasons given above, Appellants ask that the rejection of claims 1, 4, 7-9, 11, 12, 23, 28-31 and 33-36 be reversed.

Appellants hereby request that any additional fees required for timely consideration of this appeal brief be charged to **Deposit Account No. 06-1448, SMI-005.01.**

Respectfully submitted,
FOLEY HOAG LLP

Date: April 14, 2010
Foley Hoag LLP
155 Seaport Blvd.
Boston, MA 02210-2600
Telephone: 617-832-1230
Facsimile: 617-832-7000

/Hilary Dorr Lang/
Hilary Dorr Lang, Reg. No. 51,917
Attorney of Record

Claims Appendix

1. (**Previously presented**) A controlled release pharmaceutical delivery composition which provides sustained delivery of a pharmaceutically active substance for a predetermined period of time, said composition comprising;

- about 1-50% by weight polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol;

- about 1 to 58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose;

- between 0 and 10 % by weight talc;

- between 0 and 10 % by weight magnesium stearate; and

-about 1-80% by weight of a pharmaceutically active agent;

wherein said acrylic acid crosslinked polymers, hydroxyethyl cellulose and hydroxypropyl methylcellulose, talc, magnesium stearate and pharmaceutically active agent are provided as a homogenous mixture.

2-3. (**Canceled**).

4. (**Previously presented**) The composition of claim 1, wherein said polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol are carboxyvinyl polymer resins.

5-6. (**Canceled**).

7. (**Previously presented**) The composition of claim 1, wherein said composition is film coated with about 0.5 to 50% by weight of a coating material comprising anionic polymers based on methacrylic acid and methacrylic acid esters or neutral methacrylic acid esters with trimethylammonioethyl methacrylate chloride or cellulose esters.

8. (**Previously presented**) The composition of claim 1, wherein said composition additionally comprises between 0 and 95 % by weight granulating and tableting aids.

9. (**Previously presented**) A controlled release pharmaceutical delivery composition which provides sustained delivery of a pharmaceutically active substance for a predetermined period of time, said composition comprising;

- about 1 to 58% by weight of a mixture of hydroxyethylcellulose and hydroxypropylmethyl cellulose;

- about 1 to 60% by weight of ethylcellulose;

- about 1 to 80% by weight of at least one carboxyvinyl polymer resin;

- between 0 and 10% by weight of talc;

- between 0 and 10% by weight of magnesium stearate;

- between 0 and 95% by weight granulating and tableting aids; and

-about 1-80% of a pharmaceutically active agent,

wherein said hydroxyethylcellulose, hydroxypropylmethyl cellulose, ethylcellulose, carboxyvinyl polymer resin, talc, magnesium stearate, granulating and tableting aid, and pharmaceutically active agent are provided as a matrix.

10. (**Canceled**).

11. (**Previously presented**) The composition of claim 9, wherein said pharmaceutically active agent is selected from the group consisting of naproxen, COX2 inhibitors, budesonide, venlafaxine, metoprolol, carbidopa, levodopa, carbamazepine, ibuprofen, morphine, pseudoephedrine, paracetamol, cisapride, pilocarpine, methylphenidine, nicardipine, felodipine, captropril, terfenadine, fenofibrate, aciclovir, zidovudine, moclobemide, potassium chloride, lamotrigine, cladribine, loratadine, pancrelipase, lithium carbonate, orphenadrine, procainamide, ferrous sulfate, risperidone, clonazepam, lovastatin, simvastatin, pravachol, ketorolac, hydromorphone, ticlopidine, seligiline, alprazolam, divalproex and phenytoin.

12. (**Previously presented**) The composition as claimed in claim 1 wherein, said composition additionally comprises one or more pharmaceutical excipients selected from the

group consisting of lactose, silicone dioxide, sodium lauryl sulphate, calcium phosphate, calcium sulphate, silicified microcrystalline cellulose, gelucire® and compritol®.

13-22. (**Canceled**).

23. (**Previously presented**) A pharmaceutical composition comprising;

- about 1 to 80% by weight pharmaceutically active agent;

- about 1 to 50% by weight of polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol; and

- about 1 to 58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose; wherein said polymers of acrylic acid, hydroxyethyl cellulose and hydroxypropyl methyl cellulose, and pharmaceutically active agent are provided as a homogenous mixture.

24-27. (**Canceled**).

28. (**Previously presented**) The composition of claim 23, wherein said composition is film coated with about 0.5 to 50% by weight of a pharmaceutically acceptable film coating comprising anionic polymers based on methacrylic acid and methacrylic acid esters or neutral methacrylic acid esters with trimethylammonioethyl methacrylate chloride or cellulose esters.

29. (**Previously presented**) The composition of claim 23, wherein said pharmaceutically active agent is selected from the group consisting of naproxen, COX2 inhibitors, budesonide, venlafaxine, metoprolol, carbidopa, levodopa, carbamazepine, ibuprofen, morphine, pseudoephedrine, paracetamol, cisapride, pilocarpine, methylphenidine, nicardipine, felodipine, captropril, terfenadine, fenofibrate, aciclovir, zidovudine, moclobemide, potassium chloride, lamotrigine, cladribine, loratadine, pancrelipase, lithium carbonate, orphenadrine,-procainamide, ferrous sulfate, risperidone, clonazepam, lovastatin, simvastatin, pravachol, ketorolac, hydromorphone, ticlopidine, seligiline, alprazolam, divalproex and phenytoin.

30. (**Previously presented**) A pharmaceutical composition comprising:

- about 1 to 80% pharmaceutically active agent;

- about 1 to 58% by weight of hydroxyethylcellulose and hydroxypropylmethyl cellulose;

- about 1 to 60% by weight of ethylcellulose;

- about 1 to 50% by weight of at least one carboxyvinyl polymer resin;

- between 0 and 10% by weight of talc;

- between 0 and 10% by weight of magnesium stearate; and

- between 0 and 95% by weight granulating and tableting aids, wherein said pharmaceutically active agent, hydroxyethyl cellulose and hydroxypropyl methylcellulose, ethylcellulose, talc, magnesium stearate, and granulating and tableting aids, are provided as a homogenous mixture.

31. (**Previously presented**) The composition of claim 30, wherein said tableting and granulating aids are selected from the group consisting of silicone dioxide, lactose, microcrystalline cellulose, calcium phosphate and mannitol.

32. (**Canceled**).

33. (**Previously presented**) A pharmaceutical composition comprising;

- about 1 to 80% by weight pharmaceutically active agent;

- about 1 to 50% by weight of polymers of acrylic acid crosslinked with polyalkenyl alcohols or divinyl alcohol;

- about 1 to 58% by weight of a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose; wherein said polymers of acrylic acid, hydroxyethyl cellulose and hydroxypropyl methylcellulose and the pharmaceutically active agent are provided as a homogenous mixture; and

- about 0.5 to 50% by weight of a coating material coating said matrix, said coating material comprising anionic polymers based on methacrylic acid and methacrylic acid esters or neutral methacrylic acid esters with trimethylammonioethyl methacrylate chloride or cellulose esters.

34. (**Previously presented**) The composition of claim 1, comprising 1 to 25 % of hydroxyethyl cellulose.

35. (**Previously presented**) The composition of claim 1, comprising 1 to 35 % hydroxypropyl methylcellulose.

36. (**Previously presented**) The composition of claim 1, comprising 1 to 25 % of hydroxyethyl cellulose and 1 to 35 % hydroxypropyl methylcellulose.

(9) Evidence Appendix

Appendix A is a copy of the Declaration under C.F.R. § 1.132 by Odidi et al. submitted on September 21, 2004, as Attachment 1.

Appendix B is a copy of the Declaration under C.F.R. § 1.132 by Odidi et al. submitted on September 21, 2004, as Attachment 2.

Appendix C is a copy of the the Declaration under C.F.R. § 1.132 by Odidi et al. submitted on May 15, 2009.

Appendix A

Attachment 1

Attorney Docket SMI-005.01

Certificate of First Class Mailing

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450, on the date set forth below

September 21, 2004 By: Melissa Dunkel
Date of Signature and Mail Deposit

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Isa Odidi and Amina Odidi	:	Paper No.:
Serial No.	09/166,701	:	Group Art Unit: 1617
Filed:	October 5, 1998	:	Examiner: Webman, Edward J.
For:	**Controlled Release Pharmaceutical Delivery Device and Process For Preparation Thereof**		

DECLARATION UNDER 37 C.F.R. 1.132

Box Fee Amendment
Commissioner for Patents
Washington, DC 20231

Isa Odidi and Amina Odidi declare that:

1. They are co-inventors of and are familiar with the present U.S. Patent Application Serial No. 09/166,701, and they are familiar with the Official Actions issued in the present application and the reference cited by the Examiner; U.S. Patent No. 4,610,870 to Jain *et al.*

2. The controlled release pharmaceutical device and the pharmaceutical composition of the present invention comprise, amongst other components, hydroxyethylcellulose and hydroxypropylmethyl cellulose.

3. U.S. Patent No. 4,610,870 to Jain *et al.* is directed to a controlled release pharmaceutical formulation containing a core portion. The core includes a medicament and a hydrocolloid gelling agent. The hydrocolloid may comprise cellulose polymers which are cellulose ethers such as methyl cellulose, cellulose alkyl hydroxylates such as

hydroxypropylmethyl cellulose, hydroxypropylcellulose, hydroxymethylcellulose or hydroxyethylcellulose.

4. In order to demonstrate that cellulose derivatives are not interchangeable with respect to the present invention, data is provided in Tables 1 and 2 for hydroxypropylmethyl cellulose (HPMC), ethylcellulose (EC), and hydroxyethylcellulose (HEC).

Table 1 Formulation of Model Drug using Different Cellulose Derivatives

Formulation	**HPMC 15%**	**HEC 15%**	**EC 15%**
Model Drug	50%	50%	50%
HPMC	15%	0%	0%
HEC	0%	15%	0%
EC	0%	0%	15%
Lactose	44%	44%	44%
Magnesium Stearate	1%	1%	1%

Table 2 Results from Dissolution studies of the Model Formulations

Time	HPMC 15%	HEC 15%	EC 15%
0	0	0	0
1	16.9	60	88.1
2	25	68	88.2
4	43	75.6	88.3
5	50	78.4	88.4
6	53.4	80	88.5
7	63.3	83.5	88.6
8	66.5	83.2	88.6
10	78.4	88.8	90
11	80.4	87.5	90
12	81.2	84.7	90
13	89.7	90	90
14	92	90	90

5. The amount of drug released in 1 hour is 17% for HPMC, 60% for HEC and 88% for EC. It was also observed that EC tablets broke up in 30 minutes. The time taken for 70% of the drug (i.e., $T_{70\%}$) to be released was about 9 hours for HPMC, 4 hours for HEC and 30 minutes for EC. These results clearly indicate that HPMC, HEC and EC are not interchangeable.

6. These results show that the release rates of the drug depends on the cellulose polymer used. Therefore, since these tests show that cellulosic polymers listed in U.S. Patent No. 4,610,870 to Jain *et al.* are not equivalent in combination with the present invention, one skilled in the art would not assume equivalency of the listed cellulose polymers in combination with the present invention.

7. Isa Odidi and Amina Odidi further declare that all statements made herein of his/her own knowledge are true and that all statements made on information and

belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

4 November ,2003

Isa Odidi

November 4 , 2003

Amina Odidi

Appendix B

Attachment 2

Attorney Docket SMI-005.01

Certificate of First Class Mailing

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450, on the date set forth below

September 21, 2004 By: Marian Oadid
Date of Signature and Mail Deposit

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Isa Odidi and Amina Odidi	:	Paper No.:
Serial No.	09/166,701	:	Group Art Unit: 1617
Filed:	October 5, 1998	:	Examiner: Webman, Edward J.
For:	**Controlled Release Pharmaceutical Delivery Device and Process For Preparation Thereof**		

DECLARATION UNDER 37 C.F.R. 1.132

Box Fee Amendment
Commissioner for Patents
Washington, DC 20231

Isa Odidi and Amina Odidi declare that:

1. They are co-inventors of and are familiar with the present U.S. Patent Application Serial No. 09/166,701, and they are familiar with the Official Actions issued in the present application and the reference cited by the Examiner; U.S. Patent No. 4,610,870 to Jain *et al.*

2. The controlled release pharmaceutical device and the pharmaceutical composition of the present invention comprise, amongst other components, hydroxyethylcellulose (HEC) and hydroxypropylmethyl cellulose (HPMC).

3. In order to demonstrate that hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) are not interchangeable when each are used with

hydroxypropylmethyl cellulose (HPMC), data is provided in Tables 1 and 2 and in Figure 1 for the HPC/HPMC combination compared to the HEC/HPMC combination.

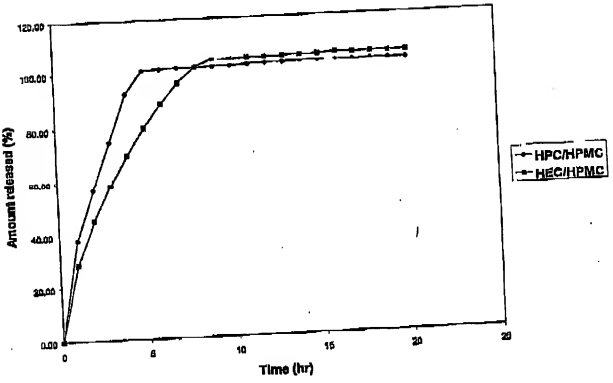
Table 1 Formulation of Model Drug using the Combination of HPC/HPMC vs. HEC/HPMC

Formulation	7.5% HPC and 7.5% HPMC	7.5% HEC and 7.5% HPMC
Model Drug	40%	40%
HPMC	7.5%	7.5%
HPC	7.5%	0%
HEC	0%	7.5%
Lactose	44%	44%
Magnesium Stearate	1%	1%

Table 2 Results from Dissolution studies of the Model Formulations

Time	7.5% HPC and 7.5% HPMC	7.5% HEC and 7.5% HPMC
0	0.00	0.00
1	38.03	28.71
2	56.72	45.27
3	74.81	58.44
4	92.49	69.71
5	100.97	79.9
6	100.97	88.46
7	101.09	95.75
8	101.09	101.33
9	101.39	104.77
10	101.50	104.59
11	101.86	104.71
12	102.10	104.89
13	102.27	105.07
14	102.45	105.18
15	102.61	105.30
16	102.69	105.66
17	102.81	105.66
18	102.87	105.66
19	102.93	105.66
20	102.93	105.66

Figure 1 Dissolution Profiles of Model Formulations



4. The results shown in Table 2 and Figure 1 show significant differences between the release profiles of the two formulations. The amount of drug released in 1 hour is 38% for the HPC/HPMC combination, while the amount of drug released in 1 hour is only 28% for the HEC/HPMC combination. The difference between the two combinations increases with time. For example, the amount of drug released in 4 hours is greater than 90% for the HPC/HPMC combination, while the amount of drug released in 4 hours is less than 70% for the HEC/HPMC combination. Furthermore, it takes 5 hours to release 100% of the drug for the HPC/HPMC combination, while it takes 8 hours before 100% of the drug is released for the HEC/HPMC combination.

5. These results show significant differences in the effect of drug release and availability of the two formulations and clearly indicate that HEC and HPC are not interchangeable when used in combination with HPMC.

6. The differences between the two formulations can impact the decision as to how often a product ought to be taken daily in order to be effective, which also impacts on patient compliance and wellness. These differences also impact adverse effects or safety especially for high potency drugs with low therapeutic indices.

7. Isa Odidi and Amina Odidi further declare that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

June 8 2004

Isa Odidi

June 8 2004

Amina Odidi

Appendix C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Isa Odidi *et al.*

Application No.: 09/166,701 Confirmation No.: 9432

Filed: October 5, 1998 Art Unit: 1614

For: CONTROLLED RELEASE PHARMACEUTICAL DELIVERY DEVICE AND PROCESS FOR PREPARATION THEREOF

Examiner: S. V. Gembeh

DECLARATION UNDER 37 C.F.R. § 1.132

1. Isa Odidi and Amina Odidi hereby declare as follows:

2. We are co-inventors of and are familiar with the present U.S. Patent Application Serial No. 09/166,701 ("the '701 application"), including the presently pending claims, and we are familiar with the Office Action mailed on November 13, 2008 ("the Office Action"), in the present application.

3. We have also reviewed the documents cited by the Examiner in the Office Action, namely U.S. Patent No. 4,252,786 to Weiss et al. ("Weiss") and U.S. Patent No. 4,940,587 to Jenkins et al. ("Jenkins").

4. Weiss describes a two-step process to make a controlled release dosage form containing two compartments. The first is an inner compartment made of a matrix core containing the drug and the second is an outer coating made of a polymer film coat comprising a combination of polymers to modify the drug release rate. Thus, the Weiss tablets are compartmentalized. They have an inner core comprising the drug and outer core comprising a polymer film coat.

5. The present claims, in contrast to Weiss, are directed to a controlled release pharmaceutical composition, wherein all of the recited components, including the drug, are provided as a homogenous mixture.

6. We have conducted experiments to establish that the release rate profile of the presently claimed composition is different from the release rate and profile of the composition described by Weiss. As discussed below, two formulations of controlled release Metformin HCl where made: one according to the present application and the other according to Weiss.

7. Table 1 shows a formula according to the present application, notably 20% of hydroxyethyl cellulose and 35% of hydroxypropylmethyl cellulose were homogenously blended with carbovinyl polymer (Carbopol), metformin HCl and the other excipients to form a homogenous blend. The homogenous blend was compressed to form tablets of 200 mg weight.

8. A formula according to Weiss et al's teachings are shown in Tables 2 and 3. Table 2 shows content of the inner matrix tablet, while Table 3 shows content of the outer ruptureable coat. Tablets weighing 90mg were made out of the inner matrix tablet mixture. These contained 20 mg Metformin HCl, but did not contain hydroxyethyl cellulose and hydroxypropylmethyl cellulose. Following Weiss et al's teachings, the 90 mg tablets were then coated with hydroxyethyl cellulose and hydroxypropylmethyl cellulose to bring the total weight per tablet to 200 mg.

9. Thus, the tablets according to the present invention and those according to the teaching of Weiss et al, contain the same type of ingredients in the same amounts, except that in the case of the Weiss et al tablets, hydroxyethyl cellulose and hydroxypropylmethyl cellulose are not in a homogenous blend with the rest of the materials that make up the Weiss tablets, ie., they are in a separate compartment.

10. Table 4 and Figure 1 show the dissolution of each of the above examples over a 13 hour period of time. The Weiss tablet releases the drug in a two step process, i.e., there is a lag phase of nearly 1 hour before the drug begins to be released from the tablet, followed by a faster rate of drug release (a dual drug release mechanism). Thus, the function of the outer coat seems to be that of slowing initial phase of drug release.

11. On the contrary, the present application approach surprisingly results in drug being released in a one step process in which drug is released over time without a lag phase (see Figure 1). Table 5 and Figure 2 show results from an example of the teaching of Weiss et al taken from US Patent 4,252,786 (Weiss). These results are in agreement with the above discussions.

12. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Isa Odidi

Dated: 11 May 2009 Signature: _____

Amina Odidi

Dated: May 11, 2009 Signature: _____

Appendix

Table 1.
Formula for tablets made from a Homogenous blend in accordance with the '701 application.

Materials	**%**	**g/ 1000g batch**	**g/ 5000g batch**
Metformin HCl	10	100	500
Lactose	19.5	195	975
Hydroxypropyl methyl cellulose	35	350	1750
Hydroxyethyl cellulose	20	200	1000
Cabopol	7	70	350
MCC	8	80	400
Magnesium Stearate	0.5	5	25
Grand Total	**100**	**1000**	**5000**

Formulation prepared according Weiss et al US Patent #: 4252786

Table 2
I. Formula for the inner Matrix tablet Core

Materials	%	g/ 1000g batch	g/ 5000g batch
Metformin HCl	22.22	100	500
Lactose	43.33	195	975
Hydroxypropyl methyl cellulose	0	0	0
Hydroxyethyl cellulose	0	0	0
Cabopol	15.56	70	350
MCC	17.78	80	400
Magnesium Stearate	1.11	5	25
Total	100	450	2250

Matrix tablet core cach weighing 90mg was made according to Weiss et al, US Patent #: 4252786

Table 3
II. Formula for the outer rupturable film coat

Materials	%	g/ 1000g batch	g/ 5000g batch
Hydroxypropyl methyl cellulose	63.64	350	1750
Hydroxyethyl cellulose	36.36	200	1000
Ethyl alcohol	Quantity sufficient	Quantity sufficient	Quantity sufficient
Total	100	550	2750
Grand Total		**1000**	**5000**

Sufficient to coat the inner matrix tablet core to a final weight of 200mg

Table 4

Comparative dissolution for Metformin hydrochloride controlled release tablets made according to the present application and those made according to Weiss.

Time[hr]	Metformin made according to US Patent App. No. 09/166701 (Odidi) (%)	Metformin made according to US Patent #: 4252786 (Weiss) (%)
0	0	0
1	43	7
2	60	59
3	71	84
4	78	94
5	83	98
6	87	102
7	89	105
8	91	105
9	92	105
10	93	105
11	94	105
12	94	105
13	96	105

Figure 1

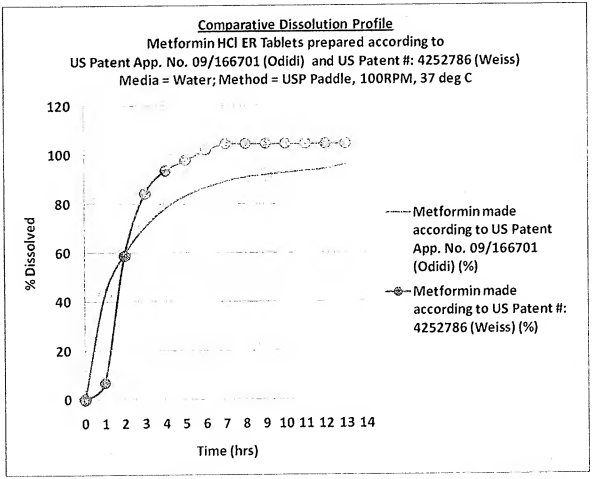
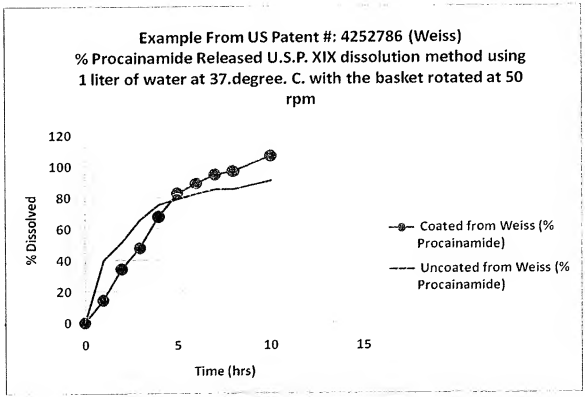

Comparative Dissolution Profile
Metformin HCl ER Tablets prepared according to
US Patent App. No. 09/166701 (Odidi) and US Patent #: 4252786 (Weiss)
Media = Water; Method = USP Paddle, 100RPM, 37 deg C
% Dissolved
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (hrs)
Metformin made according to US Patent App. No. 09/166701 (Odidi) (%)
Metformin made according to US Patent #: 4252786 (Weiss) (%)

Table 5
Comparative dissolution at different time intervals for Procainamide hydrochloride controlled release dosage example taken from US Patent #: 4252786 (Weiss)

Time Hrs	Coated from Weiss (% Procainamide)	Uncoated from Weiss (% Procainamide)
0	0	0
1	14.6	40
2	34.7	51.8
3	48	66.2
4	68	76
5	83	79.6
6	89.3	82.8
7	95	85.8
8	97.1	85.8
10	107	91.2

Figure 2



(10) Related Proceedings Appendix

None.